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HEMOSTATIC STICKING PLASTER
[Shiketsuyo bansoko]

Yasushi Shimomura, et al.

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INVENTOR	(72):	SHIMOMURA, YASUSHI; AKIBA, YOSHIKAZU.
APPLICANT	(71):	UBE IND LTD
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Specification /347*

1. Name of this Invention

HEMOSTATIC STICKING PLASTER

2. Claim(s)

[1] Cross-linked sponge prepared by (a) a step of foaming a gelatin and/or collagen solution and freeze-drying the foamed solution to obtain a sponge and (b) a step of cross-linking gelatin and/or collagen by soaking the created sponge in an organic solvent solution used as a cross-linking agent.

[2] Hemostatic sticking plaster prepared by bonding the cross-linked sponge according to the Claim 1 to an adhesive tape.

[3] Hemostatic sticking plaster according to the Claim 2 wherein a water-absorbent polymer layer is provided around the cross-linked sponge.

3. Detailed Explanation of this Invention

[Technological Field]

This invention pertains to a hemostatic sticking plaster applied to a stab wound, cut, injection needle wound, etc. in order to stop the bleeding.

[Conventional Technology and its Problems]

When conducting an artificial dialysis, instillation, blood transfusion, etc., an intravenous injection is given to a certain

*Numbers in the margin indicate pagination in the foreign text.

part of a body in order to supply blood, nutrients, etc. Since these operations commonly take a long time, considerable bleeding occurs after removing the needle from the body.

Conventionally, in order to suppress the amount of bleeding at the injected site, absorbent cotton or the like is applied to the bleeding area using an adhesive plaster so as to absorb the blood by the absorbent cotton. The problem with this method is that it cannot assure the absorbent cotton to stay at the exact bleeding site of the body, frequently causing dislocation of the cotton, failing to properly cover the bleeding site. Moreover, since the absorbent cotton itself does not function as a hemostatic agent, bleeding tends to last for a long time.

In recent years, a sponge type hemostatic agent made of gelatin or collagen is utilized. This type of hemostat is available and applied at the sutured location of an organ at the time of surgery in order to arrest the bleeding. Since the exact bleeding location of the sutured site of an organ is unclear, and gradual and continuous bleeding occurs from the surgery location, the regular hemostatic methods (i.e., burning method, suturing method, pressure method) /348 are hardly effective. However, gelatin and collagen functioning as hemostats alone can effectively absorb blood when prepared as sponges. In addition, these sponges are easily dissolvable and absorbable in the body and function as proper hemostats when buried at the sutured site of an organ in a body. Nonetheless, these sponges do not

function well as hemostats when applied to the injection location, since they are absorbable in blood.

To solve these problems, gelatin and collagen sponges are cross-linked in order to make them hard to dissolve. The mainstream of a cross-linking technique applied to a hemostat sponge is that a cross-linking agent is directly added to a gelatin or collagen aqueous solution to cause cross-linking, foamed, and freeze-dried. The problem with this technique is that, by increasing the rate of cross-linking of gelatin or collagen solution, the solution is gelled and not liquefied even when heated. Therefore, the regular method of stirring, foaming, and freeze-drying is extremely difficult to perform. When the cross-linking rate is lowered for preventing the gelling, intended improvement of anti-dissolving characteristic of the sponge is not provided.

[Technological Methods to Solve the Problems]

The present invention relates to a cross-linked sponge prepared by increasing the cross-linkage of the gelatin and/or collagen sponge in order to provide a characteristic of not easily dissolved in blood or body fluids. Also, this invention relates to a hemostatic sticking plaster prepared from this sponge.

The cross-linked sponge of this invention is prepared by cross-linking a gelatin and/or collagen sponge using a cross-linking agent.

The cross-linked sponge of this invention can be prepared by the following method: (a) A surfactant is added to an aqueous solution

of gelatin and/or collagen (hereafter, called as gelatin or the like); (b) after foaming this solution by stirring the solution or blowing an inert gas (e.g., nitrogen) into the solution, the foamed solution is freeze-dried to obtain a sponge; and (c) this sponge is soaked in an organic solvent solution containing a cross-linking agent in order to cross-link the gelatin or the like.

The production of cross-linked sponge of this invention requires the creation of a sponge by foaming/freeze-drying a gelatin solution or the like prior to cross-linking the solution. As described in the section of conventional technology and its problems, when a cross-linking agent is directly added to a gelatin solution or the like, the solution becomes jelly-like and solidified. Heating this solution further progresses the cross-linking of this solution and further hardens the solution, subsequently making it almost impossible to foam the solution by stirring, etc.

Hereafter, the production method of the cross-linked sponge of this invention will be explained in detail.

First, gelatin or the like is dissolved in water. As an aqueous solution of gelatin or the like becomes jelly-like and solidifies at room temperature, the dissolving process is preferably performed at 30 - 40°C for gelatin, and at 20 - 40°C for collagen. The concentration of gelatin or the like must be 1 - 50 wt. %, where the concentration ratio of 5 - 30 wt. % is more preferred. The concentration ratio of gelatin and the like significantly affects the

softness of the cross-linked sponge. If the concentration ratio of gelatin or the like is high, the obtained cross-linked sponge becomes hard. On the other hand, a low concentration ratio of gelatin or the like can produce a soft cross-linked sponge. However, if the ratio of gelatin or the like is below 1 wt. %, a satisfactory sponge cannot be produced, whereas the ratio exceeding 50 wt. % makes the produced sponge too hard. Therefore, these ratios should be avoided.

Next, a surfactant is added to the above-mentioned gelatin solution or the like to cause foaming using a method of high speed stirring, etc. The proper amount of surfactant is 0.1 - 30% by wt. of the aqueous solution. The preferable stirring speed is 3,000 - 30,000 rpm. The proper stirring duration is 10 - 600 seconds.

In addition to the above-mentioned high speed stirring, an inert gas may be blown into the gelatin solution for foaming of the solution. As another method, a carbon gas producing agent (e.g., sodium bicarbonate) consisting of carbon salt and succinic acid may be mixed in the above-mentioned gelatin solution or the like so as to cause foaming of the solution ~~by the produced carbon gas.~~

Then, this foamed solution is poured in a mold or extruded to form a cylindrical shape to mold the solution and freeze-dried. /349

The prepared sponge may be used as is or sliced to 0.5 - 1.0 mm thick pieces and immersed in an organic solvent solution of a cross-linking agent to cross-link the sponge. The amount of cross-linking agent in the cross-linking solution is preferably 0.0001 - 10.0 mol

per 1 g of gelatin or the like. If an amount of cross-linking agent is 0.0001 mol or less per 1 g of gelatin or the like, the prepared cross-linked sponge is easily dissolved in blood or body fluids. The proper cross-linking duration is several minutes - several hours. The room temperature is sufficient for cross-linking. By performing those operations, the cross-linked sponge of this invention can be produced.

As the gelatin or the like used to produce the cross-linked sponge of this invention, any gelatin or collagen usually used for medical purposes can be used as is, or it may be denatured by acid or alkali.

Examples of surfactant are: anionic surfactants, such as sodium lauric sulfuric acid, sodium myristic sulfuric acid, etc.; positive ionic surfactants, such as 4^{th} class ammonium salt; nonionic surfactants, such as polyethylene glycol alkyl ether, sorbitane fatty acid ester, coconut oil collagen, peptide alkali metallic salt; and combination of these materials. Among these surfactants, coconut oil collagen peptide potassium salt is most preferred considering its safeness and foaming effectiveness.

As a cross-linking agent, any cross-linking agents normally used for cross-linking (e.g., aldehyde materials, glycidyl ether materials, isocyanate materials, etc.) may be used. However, considering the residual safety, etc., aldehyde materials, such as glyoxal or glutaraldehyde, are preferred.

As an organic solvent for dissolving a cross-linking agent, any organic solvent may be used as long as it can dissolve a cross-linking agent without dissolving gelatin or the like. However, considering the safeness of the material, alcohol materials are most preferred.

A water-absorbing polymer layer may be provided around the cross-linked sponge when the cross-linked sponge of this invention is bonded to an adhesive tape.

Figs. 1 - 6 are diagrams showing the examples of hemostatic sticking plaster of this invention. Figs. 1 - 3 are hemostatic sticking plasters prepared by simply bonding the above-mentioned cross-linked sponge to an adhesive tape. Fig. 1 is a diagram illustrating the condition when the peelable tape part of hemostatic sticking plaster is peeled off. Fig. 2 is a cross-sectional diagram illustrating the section A-A′ of the same hemostatic sticking plaster. Fig. 3 is a diagram illustrating the hemostatic sticking plaster with the peelable tape.

Figs. 4 - 6 are diagrams illustrating a hemostatic sticking plaster to which a water-absorbing polymer layer is formed. Fig. 4 is a diagram illustrating the condition when a peelable sheet is peeled from this hemostatic sticking plaster. Fig. 5 is a cross-sectional diagram illustrating the section A-A′ of the same hemostatic sticking plaster.

Fig. 6 is a diagram illustrating a hemostatic sticking plaster bonded to a peelable tape.

In the figures, the reference numeral 1 denotes a cross-linked sponge; 2 denotes an adhesive tape; 3 denotes an adhesive agent layer of adhesive tape **2**; 4 denotes a peelable tape; and 5 denotes a water absorbing polymer layer.

The blood bleeding from the wound is mostly arrested by the cross-linked sponge **1**. The cross-linked sponge **1** is fixed onto the injection needle wound by the adhesive tape **2**. The cross-linked sponge **1** is adhered onto the adhesive tape **2** with a sticking agent or adhesive agent. The peelable tape **4** protects the adhesive agent layer **3**, cross-linked sponge **1**, and water-absorbent polymer layer **5** of the hemostatic sticking plaster before use. The water-absorbent polymer layer **5** absorbs blood when the bleeding exceeds the blood-arrest capacity of cross-linked sponge **1** in order to prevent the blood from leaking from the hemostatic sticking plaster. The water absorbent polymer layer **5** can be formed whenever needed.

The appropriate thickness of cross-linked sponge **1** is 0.5 - 10 mm. If it is thinner than 0.5 mm, the blood absorbing capacity becomes insufficient.

The adhesive tape **2** is prepared by providing an adhesive layer **3** to an elastic plastic film. The adhesive agent may be any regular material used for sticking tapes.

As the water absorbent polymer layer **5**, water absorbent polymers, such as salts of polymethacrylic acid, polyacrylic acid, and the like, monomethyl cellulose, etc., are used.

[Operational Example] /350

Hereafter, operational examples of this invention will be explained.

Operational example 1:

30 g of pharmaceutical gelatin (E-170, product of Miyagi Kagaku) were swollen in 200 ml of sterilized water and left untouched for 4 hours. Then, the swollen gelatin was heated to 40°C and dissolved to prepare a gelatin aqueous solution, to which 1.5 g of coconut oil collagen peptide potassium salt were added as a surfactant. This mixture was stirred for 2 min. at 18,000 rpm by a whirling blender in order to prepare a foamed gelatin solution. This foamed gelatin solution was injected into a molding device and freeze-dried. As a result, a blocked gelatin sponge was obtained.

This gelatin sponge was cut into small pieces (diameter = 50 mm; thickness = 5 mm). 10 g of these small pieces were soaked in ethanol and stirred. Next, 0.2 g of glutaraldehyde were added in this ethanol and set for 1 hour. By vacuum-drying this gelatin sponge, a cross-linked sponge 1 was prepared.

When it was immersed in 37°C physiological salt water for 24 hours and observed, this cross-linked sponge 1 was hardly dissolved in the water.

Operational example 2:

The cross-linked sponge **1** prepared in the Operational example 1 was adhered to an adhesive tape **2** so as to prepare a hemostatic sticking plaster.

Blood was taken from a dog (mixed breed, adult female, 15 Kg) by applying an injection needle (thickness = 16 G) to a jugular vein at 50 cc/min. for 1 min. Next, after the injection needle was removed, the above-mentioned hemostatic sticking plaster was adhered and fixed to the needle-wound spot for arresting the bleeding.

As a result, the cross-linked sponge **1** used as a hemostatic sticking plaster showed slight swelling caused by the absorbed blood but was not dissolved. The bleeding completely stopped 60 seconds later.

Comparison example 1:

A gelatin sponge was created using the same method as described in the Operational example 1 except that the cross-linking process was omitted. When it was immersed in 37°C physiological salt water, this gelatin sponge was completely dissolved within a minute.

Comparison example 2:

The uncross-linked sponge prepared in the Comparison example 1 was adhered to an adhesive tape 2 to prepare a hemostatic sticking plaster.

Blood was taken from a dog (mixed breed, adult female, 15 Kg) by applying an injection needle (thickness = 16 G) to a jugular vein at

50 cc/min. for 1 min. Next, after the injection needle was removed, the above-mentioned hemostatic sticking plaster was adhered to the needle-wound so as to stop the bleeding.

As a result, the gelatin sponge of hemostatic sticking plaster showed blood-caused swelling. Although bleeding stopped 180 seconds later, the gelatin sponge was dissolved and became rod-like.

Comparison example 3:

30 g of pharmaceutical gelatin (E-170, product of Miyagi Kagaku) were swollen in 200 ml of sterilized water and left untouched for 4 hours. Then, the swollen gelatin was heated to 40°C and dissolved to prepare a gelatin aqueous solution, to which 1.5 g of coconut oil collagen peptide potassium salt were added as a surfactant. Next, when 0.2 g of glutaraldehyde were gradually added, the gelatin solution became jelly-like, causing solidification, making it impossible to perform the succeeding operations. As a result, a gelatin sponge could not be created.

[Effect of this Invention]

The cross-linked sponge of this invention prepared at a higher cross-linkage ratio than the regular cross-linked sponge is hard to dissolve in blood or body fluids. Therefore, the hemostatic sticking plaster prepared from the cross-linked sponge of this invention can be effectively used for arresting the bleeding from a needle wound or cut after conducting an artificial dialysis, instillation, blood transfusion, etc.

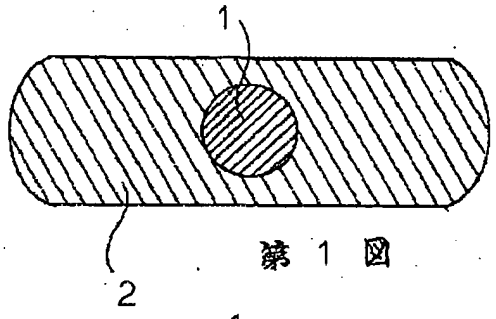
4. Simple Explanation of the Figures

Figs. 1 - 6 are diagrams showing the examples of hemostatic sticking plaster of this invention. Figs. 1 - 3 are hemostatic sticking plasters prepared by simply adhering the above-mentioned cross-linked sponge to an adhesive tape. Fig. 1 is a diagram illustrating the condition when a peelable tape of the hemostatic sticking plaster is peeled off. Fig. 2 is a cross-sectional diagram illustrating the section A-A' of the same hemostatic sticking plaster. Fig. 3 is a diagram illustrating the hemostatic sticking plaster with a peelable tape.

Figs. 4 - 6 are diagrams illustrating a hemostatic sticking plaster to which a water-absorbing polymer layer is provided. Fig. 4 is a diagram illustrating the condition when a peelable sheet is peeled from this hemostatic sticking plaster. Fig. 5 is a cross-sectional diagram illustrating the section A-A' of the same hemostatic sticking plaster. Fig. 6 is a diagram illustrating a hemostatic sticking plaster with a peelable tape.

1...Cross-linked sponge; 2...Adhesive tape; 3...Adhesive agent layer of adhesive tape 2; 4...Peelable tape; 5...Water absorbing polymer layer

Figure 1



第 1 図

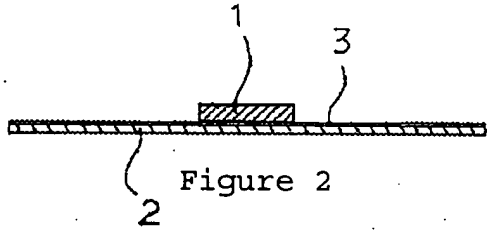


Figure 2

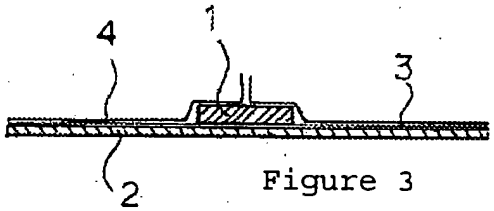
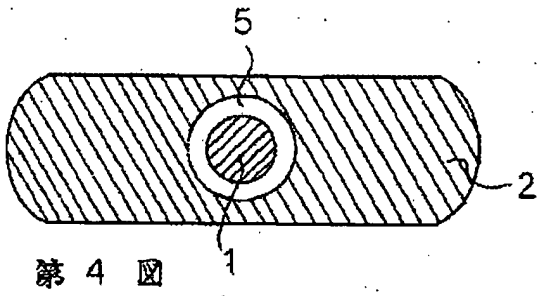


Figure 3

Figure 4



第 4 図

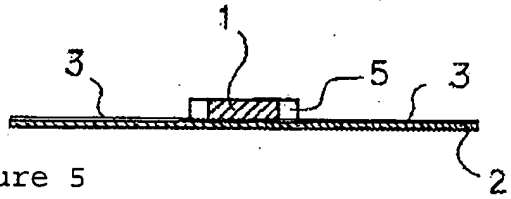


Figure 5

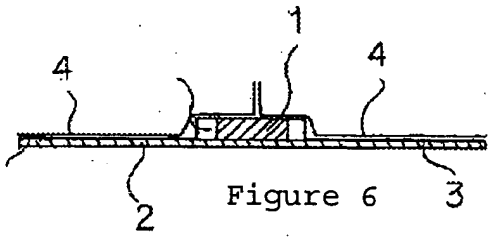


Figure 6